Central Nervous System Plasticity and Persistent Pain

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Nerve signals arising from sites of tissue or nerve injury lead to long-term changes in the central nervous system and contribute to hyperalgesia and the amplification and persistence of pain. These nociceptor activity–induced changes are referred to as central sensitization. Central sensitization involves an increase in the excitability of medullary and spinal dorsal horn neurons brought about by a cascade of events, including neuronal depolarization, removal of the voltage-dependent magnesium block of the N-methyl-D-aspartate (NMDA) receptor, calcium entry into neurons, phosphorylation of the NMDA receptor, a change in the cell's excitability, and an increase in synaptic strength. These changes also include activation of other ionotropic and metabotropic excitatory amino acid receptors, neuropeptides such as substance P, neurotrophins, and kinases involved in the phosphorylation process. Central sensitization occurs in trigeminal nociceptive pathways, and more robust neuronal hyperexcitability occurs following deep tissue stimulation than following cutaneous stimulation. By means of Fos protein immunocytochemistry, researchers have found that 2 distinct regions are activated: the subnucleus interpolaris/caudalis transition zone (Vi/Vc) and the caudal subnucleus caudalis. The latter exhibits changes very similar to those in the spinal dorsal horn, but the Vi/Vc zone likely is involved in autonomic nervous system processing and activation of the pituitary-adrenal axis. Descending systems are also an important component of the central sensitization process and provide the neural networks by which cognitive, attentional, and motivational aspects of the pain experience modulate pain transmission. These findings of nociceptor activity–induced neuronal plasticity have important clinical implications in the development of new approaches to the management of persistent pain.
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We have all experienced the pain of a needle prick. The pain is sharp but subsides quickly. We call this *acute* or *transient pain*, and it is protective: it warns us of impending tissue damage. Pain can follow athletic injuries associated with jogging or tennis. This type of pain is also protective, since it forces us to rest the injured part and avoid further damage. It usually resolves in a few days or a few weeks. However, in some cases the pain is chronic; it persists long after the injury has apparently healed, and possibly for months or years. This type of pain is nonprotective.

Studies completed in the last decade are helping to unravel the mysteries of persistent pain. We know that changes occur at the site of injury involving specialized receptors that signal tissue damage. We also know that nerve signals that arise from sites of tissue or nerve injury lead to long-term changes in the central nervous system (CNS) that contribute to hyperalgesia and the amplification and persistence of pain.

Activity-Induced Plasticity in the Central Nervous System

Both tissue and nerve injury can produce prolonged changes in the nervous system. There are distinct differences in the peripheral changes that follow tissue and nerve injury.[1] Tissue damage results in an increased sensitivity of nociceptors at the site of injury. This is called *peripheral sensitization.* The nociceptors exhibit spontaneous activity, lowered thresholds, and heightened responsiveness to subsequent painful stimuli. Thus, their response is dependent on the history of the receptor. The response is also dependent on the environment of the receptor, which changes with injury. There is a release of different chemical mediators, such as bradykinin and prostaglandins and neuropeptides such as substance P (SP); the pH is also lowered. The increased nociceptor activity leads ultimately to an increased neuronal barrage into the CNS and functional changes in the spinal cord and brain, which contribute to hyperalgesia and spontaneous pain. This is referred to as *central sensitization.*

Similarly, nerve damage can also lead to increased activity at the site of injury. But in this case, the site of injury is at the damaged nerve, not in the tissue in which the peripheral receptors are located. The connections of the nerve to the receptors have been severed. Cut or damaged nerves emit new axon sprouts and form neuromas, or bundles of axon sprouts. The neuromas emit spontaneous nerve activity, which travels to the spinal cord or brain.[2] Neuromas are also sensitive to mechanical, thermal, or chemical stimulation. Spontaneous nerve activity also originates from the cell bodies of damaged nerves, located in the dorsal root ganglia.[2] The increase in nerve activity arising from neuromas and the dorsal root ganglia results in hyperexcitability or hypersensitivity in the CNS and contributes to hyperalgesia and spontaneous pain. These changes are also called *central sensitization.* It appears that both tissue and nerve injury lead to prolonged changes in the nervous system.

The mystery of chronic pain begins at the site of injury. Nociceptive systems (those that signal approaching or actual tissue damage) have their own signature. There are specialized neurons, transmitters, and receptors in the periphery, the spinal and medullary dorsal horns, and at supraspinal sites. We now know that information about tissue damage is transmitted to the forebrain via multiple pathways, whose temporal and spatial distribution of activity ultimately results in the experience of pain.[3,4] It is important to recognize that activity in these specialized pathways is not immutable and can be modified by a number of mechanisms, which we discuss below.

Mechanisms of Central Sensitization

Signals from peripheral nociceptors travel along the smallest nerve fibers and terminate in the spinal cord and its trigeminal equivalent from the face and mouth in the medulla. The terminals of these nerve fibers release a number of chemical mediators, including glutamate, the major excitatory neurotransmitter in the dorsal horn, and such neuropeptides as SP and calcitonin gene-related peptide (CGRP). These chemical mediators contribute to an increase in the excitability of neurons in the dorsal horn of the spinal cord and medulla via actions at ionotropic receptors and G-protein–coupled receptors, leading to central sensitization.[5,6] This central sensitization involves an increase in the excitability of dorsal horn neurons brought about by a cascade of events, including neuronal depolarization, removal of the voltage-dependent magnesium block of the N-methyl-D-aspartate (NMDA) receptor, calcium entry into the cells, phosphorylation of the NMDA receptor, a change in the cell's kinetics and the resulting hyperexcitability, or an increase in synaptic strength. These changes also involve other excitatory amino acid ionotropic and metabotropic receptors, neurotrophins, and kinases involved in the phosphorylation of receptors. The critical role of NMDA receptors in central sensitization has been shown by a number of studies.[5–7] N-methyl-D-aspartate receptor antagonists that act either at the agonist recognition site or block ion channel permeability can almost completely reverse inflammatory thermal or mechanical hyperalgesia after intrathecal injection in a dose-dependent fashion.[7] In models of partial nerve injury, neuropathic thermal hyperalgesia can be attenuated by NMDA receptor antagonists,[8] but there appear to be limited effects on mechanical hyperalgesia; this reinforces the fact

that the mechanisms of inflammatory and neuropathic hyperalgesia are not identical.

The presence of ionotropic, calcium-permeable, alpha amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors in the spinal cord suggests that they may also play a role in central sensitization via calcium entry as well as interaction with the NMDA receptor. Recent studies have shown that in dorsal horn cultures and slice preparations, a majority of the gamma aminobutyric acid (GABA) and neurokinin-1 (NK-1) or SP receptor–expressing neurons also express calcium-permeable AMPA receptors.[9] These data indicate that both excitatory and inhibitory neurons may be subject to alterations in excitability via calcium-permeable AMPA receptors. Since these AMPA receptors are not subject to a voltage-dependent magnesium block, they will have a different sensitivity than NMDA receptors to depolarizing inputs.

The calcium permeability of AMPA receptors is modulated by the relative density of the glutamate receptor 2 (GluR2) subunit of the receptor, whose presence limits the calcium permeability of AMPA receptors. Zhou et al found that the induction of inflammation of the hind paw in rats led to increased expression in the spinal cord of the GluR2 flip subunit (generated by alternative splicing) at 5 hours and 1 day after injection of the inflammatory agent complete Freund's adjuvant (CFA).[10] These findings show that changes in AMPA subunit expression after inflammation may lead to modulation of the role of AMPA receptors in central sensitization.

The metabotropic glutamate receptors (mGluRs) are a family of large, monomeric receptors that are coupled to effector systems via activation of G-proteins. There are 8 mGluRs, which are further classified into 3 groups (groups I to III) according to their amino acid homology. Most studies indicate that the group I mGluR1/5 receptors are involved in nociceptive responses.[11] The role of mGluRs appears to be more prominent after the prolonged application of noxious stimuli.[12] Neugebauer et al[13] have shown that spinal mGluRs are required for the generation of inflammation-evoked spinal hyperexcitability, but they are not involved in the mediation of responses to the transient application of innocuous and noxious mechanical stimuli to noninflamed tissue. Peripheral inflammation results in upregulation of mGluR mRNA in the spinal cord.[14] Different types of excitatory amino acid receptors appear to function collectively. Metabotropic glutamate receptor agonists can facilitate activation of ionotropic NMDA and AMPA receptors. Thus, both metabotropic and ionotropic glutamate receptors play important roles in the development of central sensitization and persistent pain.

Substance P plays a role in dorsal horn hyperexcitability, presumably by increasing neuronal depolarization, releasing the magnesium block of NMDA receptors, and contributing to phosphorylation of the NMDA receptor via activation of second messenger pathways. Antagonists at the NK-1 or SP receptor, injected intrathecally, reverse inflammatory hyperalgesia in a dose-dependent fashion.[15] Mantyh et al[16] have taken advantage of the knowledge that after SP binds to its receptor, both are rapidly internalized into spinal cord neurons. They infused saporin, a cytotoxin and a ribosome-inactivating protein, into the spinal cord, conjugated to SP, and found that it destroyed spinal lamina I neurons, primarily where the SP receptor is located. Animals treated with the conjugate did not exhibit thermal or mechanical hyperalgesia after treatment.

Neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) not only contribute to establishing the development and connectivity of the nervous system, but they also play a role in sensitization after peripheral tissue injury. A number of chemical mediators in the inflammatory medium, such as cytokines (interleukin 1-beta) and tumor necrosis factor alpha, induce NGF production from keratinocytes and fibroblasts. Nerve growth factor in turn activates mast cells, which then release substances such as histamine and serotonin, which indirectly results in peripheral sensitization of nociceptors. Nerve growth factor has another important target: primary afferent neurons that express its receptor, trkA. Binding to trkA can have 2 effects: *local changes* at the site of the peripheral terminal, where the intracellular domain of trkA leads to phosphorylation of ion channels or receptors, which alters nociceptor sensitivity and peptide release, *or* retrograde transport of the NGF-trkA complex back to the dorsal root ganglia, where it alters transcription of neuropeptides involved in the sensitization process. Nerve growth factor is upregulated in the sciatic nerve after inflammation.[17] Brain-derived neurotrophic factor/mRNA is also upregulated in dorsal root ganglion neurons following adjuvant-induced inflammation.[18] The increased levels of NGF after inflammation appear to contribute to an increase in the synthesis of neuropeptides such as SP and CGRP, which ultimately participate in the development of hyperalgesia.[19,20] Importantly, the

application of NGF antibody prevents inflammatory hypersensitivity and hyperalgesia.[19,21] Woolf and Costigan[22] found recently that intraspinal injection of a fusion protein that scavenges endogenous BDNF reduces the mechanical hyperalgesia produced by inflammation. Brain-derived neurotrophic factor is expressed in dorsal root ganglion neurons, whose central terminals lie close to dorsal horn neurons that contain the receptor for BDNF (TrkB). This suggests that BDNF may act to modulate central sensitization in the spinal cord.

A Model of Neuronal Plasticity

We proposed a model a number of years ago[1] in which increased nociceptor activity at the site of tissue or nerve injury leads to spinal cord dorsal horn hyperexcitability and behavioral hyperalgesia. Although the mechanisms of increased activity arising from sites of tissue and nerve injury differ, they both produce an increased neuronal barrage that reaches the CNS. Increased neural activity from the periphery leads to increased depolarization at excitatory amino acid receptor sites. This depolarization is facilitated by neuropeptide release (SP, CGRP). The cascade of events that leads to synaptic strengthening at the NMDA receptor site is initiated, leading to central sensitization. This results in an expansion of receptive fields and hyperexcitability, which then leads to an increase in pain. This hyperexcitability, or increased depolarization, if excessive, can lead to a pathologic state by promoting excitotoxicity, cell dysfunction, and a loss of inhibitory mechanisms. The combined effects of excessive excitation and loss of inhibition further contribute to the expansion of receptive fields, hyperexcitability, and amplification and prolongation of pain.

Hyperexcitability and Central Sensitization in the Trigeminal System

Recent studies have reported the presence of central sensitization in trigeminal nociceptive pathways following noxious stimulation of the orofacial region. The neuronal hyperexcitability, manifested in part as increases in peripheral receptive field size, suggests a functional plasticity of sensory neurons. In the medullary dorsal horn (trigeminal subnucleus caudalis), stimulation of craniofacial muscle afferents results in prolonged facilitatory effects on nociceptive neurons, including the expansion of receptive fields.[23] Cutaneous formalin injection can evoke a nociceptive neuronal response that lasts for more than 30 minutes.[24] Strassman et al[25] have shown that chemical stimulation of the dural receptive fields with inflammatory mediators sensitizes the trigeminal primary afferent neurons that innervate the intracranial meninges. Further studies indicate that the sensitization of meningeal sensory neurons leads to activation and sensitization of the central trigeminal neurons, which receive convergent input from the dura and skin.[26] Local anesthesia of the dura eliminated the response to dural stimulation but had minimal effect on the increased responses to cutaneous stimulation, suggesting the involvement of a central mechanism in maintaining hyperexcitability.

Deep Versus Cutaneous Orofacial Tissue Injury

It is known that at spinal levels, C-fiber inputs produce more robust and longer-lasting neuronal hyperexcitability after muscle stimulation than after cutaneous nerve stimulation.[27] This is also the situation at the trigeminal level. There is a selective expansion of the deep mechanoreceptive fields of trigeminal nociceptive neurons after the application of mustard oil to the tongue muscle versus application to the facial skin.[28] Our recent results also demonstrate that temporomandibular joint (TMJ) tissue injury produces more robust central hyperexcitability than perioral cutaneous tissue injury.[29] When an inflammatory agent, CFA, was injected into the TMJ or perioral skin of rats, the animals developed persistent behavioral hyperalgesia associated with orofacial inflammation, resembling that seen in the hind paw inflammation model.[30,31] Inflammation of the TMJ induced significantly stronger neuronal activation than did cutaneous inflammation of perioral tissues, as indicated by trigeminal nociceptive neuronal hyperexcitability, increases in Fos protein expression (a measure of neuronal activity), and an increase in opioid gene expression.[29,32–35]

Interestingly, Fos expression induced by inflammation of the TMJ and perioral tissues paralleled the intensity and course of inflammation. This observation suggests that the increase in intensity and persistence of Fos protein expression may be associated with a maintained increase in peripheral neural input from the site of injury. As there is heavy innervation of the TMJ by unmyelinated nerve endings,[36,37] a barrage of strong nociceptive primary afferent activity is expected following inflammation. Thus, the greater Fos expression

after the application of CFA to the TMJ may reflect greater nociceptive input and greater central sensitization in contrast to the injection of CFA to perioral tissues. To test this hypothesis, we adjusted the amount of the inflammatory agent so that equivalent inflammation was induced in the TMJ and perioral regions. It was found that TMJ inflammation still produced significantly greater Fos expression in trigeminal neurons.[38] These results suggest that greater central sensitization may have also occurred in the TMJ-inflamed animal as a consequence of deep tissue inflammation.

The activation of NMDA receptors also plays an important role in trigeminal central hyperexcitability after injury. Trigeminal Fos activation after noxious stimulation is selectively attenuated by administration of NMDA receptor antagonists,[39,40] suggesting an NMDA receptor–related central sensitization at the trigeminal level. Our recent results indicate that trigeminal nociceptive neurons were more sensitive to NMDA receptor antagonists after persistent TMJ inflammation than neurons after cutaneous inflammation of perioral tissues.[41] These findings have clinical relevance. An increase in deep tissue (TMJ or muscle) C-fiber input after inflammation and strong central neuronal activation may initiate and maintain central hyperexcitability and contribute to the persistent pain associated with temporomandibular disorders (see below).

Subnucleus Interpolaris/Caudalis Transition

Using Fos protein expression as a marker of neuronal activation, researchers have found that orofacial noxious input involves 2 distinct regions in the spinal trigeminal nucleus: the subnucleus interpolaris/caudalis transition zone (Vi/Vc) and the caudal subnucleus caudalis contiguous with the upper cervical dorsal horn.[42,43] Compared to the caudal subnucleus caudalis, the role of Vi/Vc in nociceptive processing, especially in response to persistent orofacial tissue injury, is more complex. It is puzzling that in the Vi/Vc, unilateral orofacial inflammation induces bilateral Fos expression that is beyond the somatotopically defined region.[29,43] Furthermore, a very small portion of neurons recorded from the Vi/Vc are nociceptive.[44] In contrast to activity in the caudal subnucleus caudalis, Vi/Vc neuronal activity is not suppressed by morphine.[45] Both noxious and innocuous stimuli induce Fos protein expression in the Vi/Vc.[46] The stimulation-induced Fos expression in the Vi/Vc is not sensitive to morphine or NK-1 and -2 tachykinin receptor antagonists.[47,48] All these results suggest that Vi/Vc neurons may not play a major role in the sensory discriminative aspects of nociceptive processing.

Our further analysis of the Vi/Vc transition zone indicates that it consists of several components. In addition to somatotopically relevant nociceptive activation, the Vi/Vc appears to contribute to aspects of nociceptive activity, including reflex activity and autonomic responses. Unilateral orofacial inflammation–induced Fos labeling in the ventral Vi/Vc is equivalent bilaterally,[29] and previous studies indicate that neurons in the ventrolateral pole of the Vi/Vc are more likely involved in autonomic responses related to nociceptive stimulation.[49] Anesthesia alone can induce Fos labeling at this level, primarily in the ventral portion of the Vi/Vc.[29,42,50] Using CFA-induced masseter inflammation to produce Fos protein expression, we found that vagotomy and adrenalectomy selectively reduced Fos labeling at the Vi/Vc level.[50] We conclude that this hyperexcitability is part of the CNS response to peripheral tissue injury and the involvement of the autonomic nervous system and the pituitary-adrenal axis.[50]

Paratrigeminal Nucleus

Recent studies have found that the paratrigeminal nucleus may play an important role in the response to persistent TMJ tissue injury. Inflammation of the TMJ, but not cutaneous perioral tissue, induces selective and persistent Fos protein expression and preprodynorphin mRNA upregulation in the paratrigeminal nucleus.[29,34,43] The paratrigeminal nucleus is a large collection of interstitial neurons and neuropil in the spinal trigeminal tract at the level of the transition from the subnucleus caudalis to Vi.[51] It receives convergent sensory input from the head and neck as well as from the cranial portion of the alimentary tract.[52] Previous studies have demonstrated the presence of a variety of neurochemicals in the paratrigeminal nucleus, such as SP, CGRP, leu-enkephalin, and neuronal nitric oxide synthase.[52,53] Moreover, sensory input to the paratrigeminal nucleus appears to be further relayed to other nuclei implicated in central pain and autonomic pathways, such as the parabrachial nucleus and the hypothalamus.[54,55] We have shown that a portion (about 30 percent) of paratrigeminal neurons that exhibit preprodynorphin mRNA after TMJ inflammation project to the parabrachial nucleus,[56] supporting the notion that the activation of paratrigeminal neurons reflects an increase in excitability in trigeminal nociceptive pathways.

Descending Modulation

The studies we described above have focused almost entirely on the role of primary afferent neurons and intrinsic spinal cord and trigeminal brain stem neurons in dorsal horn plasticity and hyperexcitability. The role of the third major component in the spinal and medullary dorsal horns, the axon terminals of extrinsic neurons originating mainly from descending brain stem pathways, has been neglected until recently in the mechanisms of central sensitization. Descending mechanisms are important because they provide the neural networks by which cognitive, attentional, and motivational aspects of the pain experience modulate nociceptive transmission.[4]

We have shown that descending modulation increases after inflammation to modulate central sensitization, and that the effects can be both facilitatory and inhibitory. In our most recent studies,[57–59] we combined Fos protein immunoreactivity as a measure of neuronal activity in the spinal cord and behavioral models of hyperalgesia to evaluate the contribution of specific brain stem nuclei to the modulation of neuronal activity in the spinal dorsal horn. We made lesions of the nucleus raphe magnus (NRM) in the medulla by the administration of the neurotoxin 5,7-DHT, which destroys serotonin-containing axons that descend to the spinal dorsal horn. Then, 5 to 7 days after injection of the neurotoxin into the NRM, we injected the inflammatory agent CFA into the hind paw of rats. The behavioral hyperalgesia was significantly enhanced after the injection of the neurotoxin, as compared to a vehicle injection. There also was an increase in Fos protein labeling in all laminae of the spinal dorsal horn. These findings suggest that destruction of the serotonin-containing neurons in the NRM results in a reduction in the net descending inhibitory effects from the NRM on dorsal horn neurons, leading to a further increase in spinal cord central sensitization.

In contrast, lesions of nucleus gigantocellularis (NGC) in the medulla led to opposite effects. The NGC lesions were made bilaterally with ibotenic acid, which produces excitotoxic destruction of the neurons. Two to 3 days later, CFA was injected into the ipsilateral hind paw, and after 24 hours there was a reduction in the hyperalgesia and a reduction in Fos protein immunoreactivity in the spinal cord. It appears that NGC lesions have the net effect of reducing hyperalgesia, suggesting that the net descending effects from NGC are facilitatory.[58,60]

A net inhibitory effect of descending influences on hyperexcitability at the level of the spinal dorsal horn has been shown in experiments in which complete transection of the spinal cord was performed, or in which selected major descending tracts were sectioned.[57,61] It is important to remember that this is the net effect of both inhibitory and excitatory influences from supraspinal sites. In these animals, the balance is toward a net inhibition; however, it is conceivable that under different behavioral or physiologic conditions, this balance could shift to a net excitatory effect, in which descending modulation would result in greater hyperexcitability and more pain. An imbalance of these modulatory systems may be one mechanism underlying the variability in chronic pain conditions. In patients suffering from deep pain conditions, such as temporomandibular disorders, fibromyalgia, and low back pain, in which central sensitization appears to be a prominent component (see above), the diffuse nature and amplification of pain may be due in part to this imbalance.

Further Clinical Implications

These findings of activity-induced neuronal plasticity at peripheral and central nervous system sites have important clinical implications. The problem of persistent pain can now be addressed in the periphery at the site of injury and at CNS sites. Obviously, this knowledge can be used in the development of new approaches to the management of persistent or chronic pain. It also teaches us about mechanisms of pain, which can also be applied in the diagnosis of clinical conditions.

The knowledge that increases in nociceptor activity can lead to long-term hyperexcitability in the nervous system and amplification of pain has led to the use of preoperative administration of drugs that act to reduce or block activity in peripheral nociceptors, such as local anesthetics or nonsteroidal anti-inflammatory agents. Support for this idea was provided by clinical studies demonstrating that presurgical administration of local anesthetics reduced postoperative pain in comparison to surgery performed without local anesthesia[62] or postoperative infiltration of local anesthetic.[63] The efficacy of so-called "preemptive analgesia" has been questioned by others on the basis of poor experimental design or the effects of adjunctive drugs or negative results.[64] A major concern has been that these agents had effects beyond the surgical period and therefore they were

not only interfering with the neural barrage due to the surgical procedure but also with neural activity caused by the inflammatory process following surgery. By varying the time and duration of local anesthetics used in the extraction of impacted third molar teeth, a recent study was able to distinguish between intraoperative and postoperative effects on the development of pain after surgery.[65] Patients were given a short-acting local anesthetic (lidocaine) or saline preoperatively; general anesthesia was then induced and the teeth were extracted. A second set of intraoral injections was administered at the end of the surgery—either a long-acting local anesthetic (bupivacaine) or saline. This resulted in 4 groups of patients: preoperative lidocaine/postoperative saline, saline/bupivacaine, lidocaine/bupivacaine, or saline/saline. Pain over the first 4 hours was significantly lower in the 2 groups of patients who received bupivacaine postoperatively than in the other 2 groups. At 48 hours, pain was also significantly lower in these same 2 groups, and no effect was demonstrated for preoperative lidocaine. These findings indicate that the blockade of postoperative nociceptive input reduces pain long after the anesthetic effects have terminated. In contrast, there was no effect from the blockade of the intraoperative nociceptive input on postoperative pain in this model, suggesting that nociceptive input during the brief period of the surgery produced minimal central sensitization, compared to the prolonged postoperative nociceptive input. Most important, these results indicate that blocking nociceptive input from the site of injury during the postoperative period is a critical component of the analgesic process of attenuating pain following surgery.

A suggestion for ways in which our knowledge of mechanisms of persistent pain can improve our ability to manage it comes from another study.[66] The study describes the case history of a 52-year-old woman who developed severe shooting pains in the elbow following ulnar nerve transposition surgery. After 18 months of various treatments, which resulted in partial relief, she experienced severe pain in the forearm and hand. Clinical examination revealed spontaneous pain in the forearm and pain evoked by light touch from a cotton wisp on the elbow, forearm, and hand. This was diagnosed as mechanical allodynia, which was shown to be mediated by activation of large myelinated or A-beta afferent fibers normally activated by touch. This type of allodynia in animal research has been shown to be related to the development of central sensitization.[67,68] Two minutes after the injection of 1.5% lidocaine into the hyperpigmented region at the elbow, the injected site was completely anesthetized, and the allodynia had disappeared from all areas. It was proposed[66] that the A-beta–mediated allodynia resulted from input from a nociceptive focus at the original site of injury that dynamically maintained altered central processing, resulting in touch being perceived as pain. The peripheral input was thought to come from several sources: neuromas, sympathetic stimulation, or soft tissue injury. Blocking this input caused the central processing to revert to normal and eliminated the allodynia.

These clinical studies illustrate the importance of peripheral sensitization and central sensitization in mechanisms of ongoing pain. We should not think of peripheral sensitization, central sensitization, and descending modulation as pathologic changes in the nervous system, but as part of the normal function of these systems. This normal function is protective; we guard the injured site and we also recuperate and heal the injury. This protective and healing function sometimes goes awry, and the changes in the CNS may persist, even after much of the peripheral tissue injury response has returned to normal. We need to better understand the factors that contribute to such disturbances of the CNS and lead to the abnormal persistence of pain.

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